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88 USPQ2d 1849

In re Alonso

**U.S. Court of Appeals
Federal Circuit**

No. 2008-1079

Decided October 30, 2008

545 F3d 1015

Headnotes

PATENTS

[1] Patentability/ Validity — Specification — Written description (►115.1103)

Substantial evidence supports conclusion that single monoclonal antibody disclosed in specification of application directed to method for treating neurofibrosarcoma is not sufficiently representative of genus of antibodies specific to neurofibrosarcoma cells required to practice claimed treatment method, since patentee of biotechnological invention cannot necessarily claim entire genus after describing only limited number of species, and record shows that antibodies required to perform claimed method vary substantially in their composition, since applicant asserts that he reduced

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claimed method to practice and identified resulting compound, but proof of reduction to practice, absent adequate description of what is reduced to practice, does not identify invention for purposes of written description requirement, and single compound disclosed by applicant cannot be viewed as representative of densely populated genus, and since specification does not characterize antigens to which monoclonal antibodies must bind, and teaches nothing about structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to large family of antibodies implicated by claimed method.

Case History and Disposition

Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Kenneth Alonso (no. 08/469,749). Applicant appeals from decision sustaining rejection of claim in application for lack of adequate written description. Affirmed.

Attorneys

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Janet A. Gongola and Thomas W. Krause, associate solicitors, and Sydney O. Johnson Jr., acting solicitor, Arlington, Va., for Director, U.S. Patent and Trademark Office.

Judge

Before Michel, chief judge, Mayer, circuit judge, and Stearns, district judge (District of Massachusetts, sitting by designation).

Opinion Text

Opinion By:

Stearns, J.

Dr. Kenneth Alonso appeals a decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences ("Board") sustaining in part the examiner's final rejection of claim 92 of U.S. Patent Application No. 08/469,749 ("749 Application"). In its decision, the Board reversed the examiner's rejection of claim 92 for lack of enablement and sustained the rejection as invalid for lack of adequate written description. *Ex parte Alonso*, No. 2006-2148 (B.P.A.I. July 25, 2007) ("Decision"). We affirm.

I. BACKGROUND

An arsenal of antibodies generated by the immune system defends the human body against illnesses caused by bacteria and cancerous cells and other invasive agents. Antibodies are large, Y-shaped molecules secreted by white blood cells known as "B lymphocytes," or "B-cells." Antibodies are capable of binding to the surfaces of foreign cells or other substances known as "antigens." The specific location on the surface of the antigen where the antibody attaches is termed the "epitope." The arms of the Y-shaped molecule bind to the epitope with specificity. Antibodies that bind to the same epitope are said to have the same "idiotypic." Monoclonal antibodies ("MABs") are derived from a single precursor and have a single idiotypic. They are produced using "hybridoma" (fusion) technology. A human-to-human hybridoma is created by fusing a human tumor cell to an antibody-producing human B-cell, resulting in secretion by the B-cell of monoclonal antibodies with identical affinity and specificity to a given epitope on the surface of the tumor cell.

On June 6, 1995, Dr. Alonso filed the '749 Application entitled, A Method of Producing Human-Human Hybridomas, The Production of Monoclonal and Polyclonal Antibodies Therefrom, and Therapeutic Use Thereof.¹ The claimed invention recites a method for treating neurofibrosarcoma, a rare cancer of the sheath of a peripheral nerve, that uses human monoclonal antibodies targeted at a patient's tumor. Claim 92 of the '749 Application discloses

¹ Alonso claimed priority to an application he filed seven years earlier involving similar subject matter.

[a] method of treating neurofibrosarcoma in a human by administering an effective amount of a monoclonal antibody idiotypic to the neurofibrosarcoma of said human, wherein said monoclonal antibody is secreted from a human-human hybridoma derived from the neurofibrosarcoma cells.

In Example 1 of the '749 Specification, Alonso described the preparation of a tumor cell suspension from the sample of a tumor and the subsequent sensitization of human spleen cells. The sensitized spleen cells are fused with an immortalized cell line (e.g., a fetal marrow line, a lymphoblastoid line, or a plasma cell line from myeloma). The resulting cells are screened for hybridomas that secrete antibodies specifically reactive with the sensitizing tumor cells (and non-reactive with a range of other tissues and cell types). Example 2 disclosed the results of an experiment conducted by Alonso in treating Melanie Brown, a patient with neurofibrosarcoma. Adult

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spleen cells were sensitized with cells from Brown's tumor. The resulting hybridoma secreted monoclonal antibodies, which reacted with a 221 KiloDalton tumor surface antigen. The spleen line (AS-151), the lymphoblast fusion line (BM-95), and the hybridoma (HB983) were deposited with the American Type Culture Collection in September of 1998. The antibody from the hybridoma line was deposited with the Food and Drug Administration.²

² Alonso infused Brown with 100 mg of the antibody, and cancerous lesions in her lungs were cleared within twenty-four hours. In addition, Brown's brain tumor became necrotic within seven days, and she experienced a one-month regression of her cancer.

The examiner rejected claim 92 as lacking adequate written descriptive support for the broad genus of

antibodies encompassed by the claim language.

Applicant is reminded that the disclosure only describes the preparation of a single Mab produced by the hybridoma cell line HB983. However, the claims are directed toward a much larger genus of molecules (i.e., Mabs that bind to a neurofibrosarcoma), not a specific Mab identified by the deposited hybridoma.... The crux of the rejection is whether or not applicant has provided sufficient support for the broadly claimed genus of therapeutic antibodies. As set forth in the rejection, the skilled artisan would reasonably conclude that applicant was clearly not in possession of the claimed genus of compounds. Applicant should direct the claim language toward the only described embodiment (e.g., a Mab produced by hybridoma HB983).

The Board affirmed the rejection, agreeing that Alonso had not adequately described the claimed invention because the "single antibody described in the Specification is insufficiently representative to provide adequate written descriptive support for the genus of antibodies required to practice the claimed invention." *Decision*, slip op. at 7.

II. DISCUSSION

Whether an applicant has complied with the written description requirement is a finding of fact, to be analyzed from the perspective of one of ordinary skill in the art as of the date of the filing of the application. *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997); *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563 [19 USPQ2d 1111] (Fed. Cir. 1991). This Court reviews the Board's factual determinations under a substantial evidence standard. *In re Gartside*, 203 F.3d 1305, 1316 [53 USPQ2d 1769] (Fed. Cir. 2000). "Substantial evidence" is relevant evidence that "a reasonable mind might accept as adequate to support a conclusion." *Id.* at 1312 (citation omitted). In making the assessment, we examine "the record as a whole, taking into account evidence that both justifies and detracts from an agency's decision." *Id.* That a fact finder could draw "two inconsistent conclusions from the evidence does not prevent an administrative agency's finding from being supported by substantial evidence." *Id.* (citation omitted). Rather, the Board's decision must be affirmed if any "reasonable fact finder could have arrived at the [same] decision." *Id.*

The written description requirement of 35 U.S.C. § 112, ¶ 1, is straightforward: "The specification shall contain a written description of the invention" To satisfy this requirement, the specification must describe the invention in sufficient detail so "that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought." *Lockwood v. Am. Airlines, Inc.*, 107 F.3d 1565, 1572 [41 USPQ2d 1961] (Fed. Cir. 1997); see also *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 [76 USPQ2d 1724] (Fed. Cir. 2005); *Eiselstein v. Frank*, 52 F.3d 1035, 1039 [34 USPQ2d 1467] (Fed. Cir. 1995).

The requirement "serves a teaching function, as a 'quid pro quo' in which the public is given 'meaningful disclosure in exchange for being excluded from practicing the invention for a limited period of time.'" *Univ. of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 922 [69 USPQ2d 1886] (Fed. Cir. 2004) (quoting *Enzo Biochem, Inc. v. GenProbe Inc.*, 323 F.3d 956, 970 (Fed. Cir. 2002)).³ The Board framed the issue raised by the '749 Application as follows.

³ The requirement is rigorous, but not exhaustive: "[I]t is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention." *LizardTech*, 424 F.3d at 1345.

[W]hether the single monoclonal antibody described in the Specification is representative

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of the genus of monoclonal antibodies required to practice the claimed treatment method. That, in turn, depends on whether or not the antibodies (and the antigens they bind) would have been expected to vary substantially within the genus. The greater the variation in the genus, the less representative any particular antibody would be.

Decision, slip op. at 6.

The Board properly characterized the relevant genus as the "genus of antibodies specific to neurofibrosarcoma cells." *Id.* A genus can be described by disclosing: (1) a representative number of species in that genus; or (2) its "relevant identifying characteristics," such as "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Enzo*, 323 F.3d at 964.

Relying principally on two scientific articles, including one authored by Alonso himself, the Board determined that

[t]here is ample evidence of record that the specificities of antibodies falling within the scope of the genus (and the structures of the antigens they bind) would be expected to vary substantially. For example, Osband ⁴ provides evidence of a recognition in the art that considerable antigenic "heterogeneity of tumors both between patients and metastatic sites within a single patient" is to be expected. In addition, an article authored by [Alonso] ⁵ acknowledges that "[t]he efficacy of antibody therapy is thought to be related to tumor burden as well as to *idiotypic change in the original tumor*." This acknowledged heterogeneity is reflected in the goal of the claimed method — to raise customized antibodies to possibly unique antigens on a particular patient's tumor.

Finally, as discussed above, for purposes of satisfying the written description requirement, it is not enough merely to disclose a method of making and identifying compounds capable of being used to practice the claimed invention. That is, it is not enough to describe[] the procedure for making a human-human hybridoma from neurofibrosarcoma, and teach how to determine whether a given antibody, specific to a patient's neurofibrosarcoma, will function in the claimed method. We find that the single antibody described in the Specification is insufficiently representative to provide adequate written descriptive support for the genus of antibodies required to practice the claimed invention.

⁴ M.E. Osband and S. Ross, *Problems in the Investigational Study and Clinical Use of Cancer Immunotherapy*, 11 *Immunology Today* 193-95 (1990).

⁵ Kenneth Alonso, *Human-Human Monoclonal Antibody Directed Against Tumor Surface Antigen in the Treatment of Human Malignancy*, 14 *American Journal of Clinical Oncology* 463-71 (1991).

Decision, slip op. at 6-7 (internal quotation marks and citations omitted, footnotes supplemented).

[1] The Board's conclusion is supported by substantial evidence. The articles relied upon by the Board confirm the hypothesis that the antibodies required to perform Alonso's claimed method vary substantially in their composition. We have previously held in a similar context that "a patentee of a biotechnological invention cannot necessarily claim a genus after only describing a limited number of species because there may be unpredictability in the results obtained from species other than those specifically enumerated." *Noelle v. Lederman*, 355 F.3d 1343, 1350 [69 USPQ2d 1508] (Fed. Cir. 2004).

In another similar case, we evaluated claims directed to a method of determining whether a drug could selectively inhibit the activity of COX-2, a cyclooxygenase thought to be responsible for inflammation associated with arthritis. *See Rochester*, 358 F.3d at 917-18. One of the claims at issue was directed to "a method for selectively inhibiting [COX-2] activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the [COX-2] gene product to a human host in need of such treatment." *Id.* at 918. We found that the specification lacked written descriptive support, agreeing with the district court that

it is clear from reading the patent that one critical aspect of the method — a compound that selectively inhibits [COX-2] activity — was hypothetical, for it is clear that the inventors had neither possession nor knowledge of such a compound.... [T]he claimed method depends upon finding a compound that selectively inhibits [COX-2] activity. Without

such a compound, it is impossible to practice the claimed method of treatment.

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Id. at 926. We further noted that the specification contained "no disclosure of any method for making even a single 'non-steroidal compound that selectively inhibits activity of the [COX-2] gene product,'" and failed to "steer the skilled practitioner toward compounds that can be used to carry out the claimed methods." *Id.* at 928, 929.

Alonso attempts to distinguish his claimed invention from *Rochester* by emphasizing that he reduced his method to practice and identified the resulting compound. We are not persuaded by the distinction. "[P]roof of a reduction to practice, absent an adequate description in the specification of what is reduced to practice, does not serve to describe or identify the invention for purposes of [the written description requirement]." *Enzo*, 323 F.3d at 969. ⁶ Moreover, while it is true that *Rochester* disclosed no compounds that worked with the claimed method, the one compound disclosed by Alonso cannot be said to be representative of a densely populated genus.

⁶ The reduction-to-practice argument also implicates §112's enablement requirement. The Board reversed the examiner's rejection of claim 92 for lack of enablement. See *Decision*, slip op. at 12. Alonso argues that the Board's findings as to sufficiency of description and enablement are at odds with one another. It is true that the written description and enablement requirements "usually rise and fall together. That is, a recitation of how to make and use the invention across the full breadth of the claim is ordinarily sufficient to demonstrate that the inventor possesses the full scope of the invention, and vice versa." *LizardTech*, 424 F.3d at 1345. However, we have been clear that "[a]lthough the legal criteria of enablement and written description are related and are often met by the same disclosure, they serve discrete legal requirements." *Capon v. Eshhar*, 418 F.3d 1349, 1360 [76 USPQ2d 1078] (Fed. Cir. 2005). "[A]n invention may be enabled even though it has not been described." *Rochester*, 358 F.3d at 921.

In *Rochester*, we reasoned that while the specification

describes what can be done with any compounds that may potentially be identified through those assays, including formulation into pharmaceuticals, routes of administration, estimation of effective dosage, and suitable dosage forms ... the '850 patent does not disclose just which peptides, polynucleotides, and small organic molecules have the desired characteristics of selectively inhibiting [COX-2]. Without such disclosure the claimed methods cannot be said to have been described.

Rochester, 358 F.3d at 927 (internal citation and quotation marks omitted). We additionally found that *Rochester* had failed to present any evidence that one skilled in the art would have been able to isolate and identify any given compound based on *Rochester*'s "vague functional description" *Id.* at 928. Even more recently, we held that the written disclosure requirement was not met where the claims at issue covered a broad "genus of recombinant plasmids that contain coding sequences for DNA polymerase ... from any bacterial source, [but] the narrow specifications of the [relevant patents] only disclose[d] the ... gene coding sequence from one bacterial source" *Carnegie Mellon Univ. v. Hoffman-LaRoche Inc.*, 541 F.3d 1115, 1125 [88 USPQ2d 1233] (Fed. Cir. 2008) (emphasis added).

The same is true here. The specification of the '749 Application does not characterize the antigens to which the monoclonal antibodies must bind; it discloses only the molecular weight of the one antigen identified in Example 2. This is clearly insufficient. ⁷ The specification teaches nothing about the structure, epitope characterization, binding affinity, specificity, or pharmacological properties common to the large family of antibodies implicated by the method. While Alonso's claim is written as a method, the antibodies themselves are described in purely structural language — "a monoclonal antibody idiotype to the neurofibrosarcoma of said human." This sparse description of antibody structure in the claim stands in stark contrast to the detailed method of *making* the antibodies found in the specification.

⁷ It bears mentioning that the examiner encouraged Alonso to amend his claims to cover only the MAb produced by the identified hybridoma.

The *Eli Lilly* decision is also instructive. In *Eli Lilly*, the University of California laid claim to all vertebrate insulin cDNAs, including the human insulin cDNA, although it had identified only the cDNA for rat insulin. See *Eli Lilly*, 119 F.3d at 1567.⁸ We ruled that the written description requirement was not met because "a description of rat insulin cDNA is not a description of the broad classes of vertebrate

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or mammalian insulin cDNA." *Id.* at 1568. As in *Eli Lilly*, the specification of the '749 Application contains information about only one compound.⁹

⁸ The claims at issue in *Eli Lilly* were directed to "a recombinant *plasmid* replicable in [a] prokaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a *vertebrate*, which mRNA encodes insulin." *Eli Lilly*, 119 F.3d at 1563 (emphasis in original).

⁹ Alonso cites *In re Herschler*, 591 F.2d 693 [200 USPQ 711] (CCPA 1979), where our predecessor court held that the disclosure of a single corticosteroid was sufficient to describe the genus of physiologically active steroids that could be used in practicing the claimed invention. The court based its decision on the fact that the class of implicated compounds was "chemically quite similar." *Id.* at 701. Alonso argues that the same is true with respect to the antibodies generated by a patient's specific neurofibrosarcoma. However, he points to no evidence in the record corroborating his "similarity" thesis.

Apart from the representative number of species test applied by the Board, we have found adequate written descriptive support for a claimed invention where the disclosure specifies "relevant identifying characteristics," such as "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Enzo*, 323 F.3d at 964 (emphasis in original). Alonso argues that there is a well-known correlation between the structure and function of the neurofibrosarcoma-specific antibodies generated by his disclosed treatment method. He maintains that the members of the genus of antibodies directed to a particular patient's tumor share the same function — they each bind to a patient's neurofibrosarcoma, thereby bolstering the patient's immune mechanism and stimulating an attack on the tumor cells. As for structure, Alonso argues that because monoclonal antibodies are secreted from a hybridoma made from a particular neurofibrosarcoma, the antibodies are necessarily specific. He further argues that there is a "well-known correlation between human antibody structure and antibody function."

Alonso did not raise this structure-function correlation argument in the proceedings before the Board. "Failure to advance legal theories before the [B]oard constitutes a failure to 'make a complete presentation of the issues,' and permitting a party to raise those theories for the first time [after the agency has rendered its final decision] would be both inefficient and 'wasteful of administrative and judicial resources.'" *Boston Scientific Scimed, Inc. v. Medtronic Vascular, Inc.*, 497 F.3d 1293, 1298 [83 USPQ2d 1669] (Fed. Cir. 2007). Accordingly, we will not consider this newly minted argument on appeal.¹⁰

¹⁰ Even were we tempted to consider the argument, Alonso would not be entitled to relief. In *Noelle*, the applicant claimed a human monoclonal antibody (or fragment thereof) secreted from a particular hybridoma that binds to an antigen expressed on activated T-cells. The application did not, however, disclose any structural information about the human antigen. *Noelle*, 355 F.3d at 1345-46. It described only the mouse antigen. We concluded that the function-structure correlation test was not met.

If [the applicant] had sufficiently described the human form of CD40CR antigen, he could have claimed its antibody by simply stating its binding affinity for the "fully characterized" antigen. [The applicant] did not describe human CD40CR antigen. Therefore, [the applicant] attempted to define an unknown by its binding affinity to another unknown.

Noelle, 355 F.3d at 1349. As Alonso has not pointed to any structure for his claimed antibodies, there is no structure to which he may correlate the function of his claimed antibodies.

III. CONCLUSION

For the aforementioned reasons, the decision of the Board is affirmed.

AFFIRMED.

- End of Case -

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ISSN 2157-1414

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